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Multicenter phase II trial of gefitinib first-line therapy followed by chemotherapy in advanced non-small-cell lung cancer (NSCLC): SAKK protocol 19/03

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Background: Gefitinib is active in patients with pretreated non-small-cell lung cancer (NSCLC). We evaluated the activity and toxicity of gefitinib first-line treatment in advanced NSCLC followed by chemotherapy at disease progression.

Patients and methods: In all, 63 patients with chemotherapy-naive stage IIIB/IV NSCLC received gefitinib 250 mg/day. At disease progression, gefitinib was replaced by cisplatin 80 mg/m^2 on day 1 and gemcitabine 1250 mg/m^2 on days 1, 8 for up to six 3-week cycles. Primary end point was the disease stabilization rate (DSR) after 12 weeks of gefitinib.

Results: After 12 weeks of gefitinib, the DSR was 24% and the response rate (RR) was 8%. Median time to progression (TtP) was 2.5 months and median overall survival (OS) 11.5 months. Never smokers (n = 9) had a DSR of 56% and a median OS of 20.2 months; patients with epidermal growth factor receptor (*EGFR*) mutation (n = 4) had a DSR of 75% and the median OS was not reached after the follow-up of 21.6 months. In all, 41 patients received chemotherapy with an overall RR of 34%, DSR of 71% and median TtP of 6.7 months.

Conclusions: First-line gefitinib monotherapy led to a DSR of 24% at 12 weeks in an unselected patients population. Never smokers and patients with EGFR mutations tend to have a better outcome; hence, further trials in selected patients are warranted.

Key words: advanced disease, chemotherapy, first-line therapy, gefitinib, non-small-cell lung cancer

introduction

Lung cancer is a leading cause of cancer mortality and cases are expected to increase worldwide. Over 85% of lung cancer patients present with non-small-cell lung cancer (NSCLC), the majority with unresectable disease. Since the 1990s, platinum-based combination chemotherapy is the standard first-line treatment in advanced NSCLC patients with good performance status (PS) [1]. Despite some improvements, efficacy and tolerability of chemotherapy remain unsatisfactory. Response rates (RRs) to standard chemotherapy regimens are in the 20% range; about one-third of patients survive for >1 year. Platinum-based chemotherapy is associated with moderate to severe hematological and non-hematological toxic effects in a majority of patients [2].

Gefitinib is an oral, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). As second-line therapy, gefitinib produced RRs comparable to those previously reported for second-line chemotherapy [3, 4]. Main toxic effects reported in a recent phase III study were rash and diarrhea in 37% and 27%, respectively (any grade; grade III/IV 1.6% and 2.8%) [5]. Patients with adenocarcinoma, females and patients of Asian origin as well as never smokers respond particularly well. Erlotinib, a similar EGFR-TKI has been approved as second- and third-line therapy for NSCLC on the basis of improved survival when compared with placebo [6]. In a similar trial with gefitinib, however, a survival benefit was shown only in patients of Asian origin and in never smokers [5].

In 2004, two landmarks studies [7, 8] reported a correlation between response to gefitinib and *EGFR* gene mutations clustered near the adenosine triphosphate-binding pocket of

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the TK domains (exons 18–21) in patient's tumors. Further reports correlated response to EGFR-TKI's with high *EGFR* gene copy number (FISH analysis), and showed resistance in patients whose tumors harbored *KRAS* mutations [9, 10].

In this multicenter phase II trial, we assessed the efficacy and tolerability of gefitinib as first-line treatment in unselected patients with advanced NSCLC, followed by standard chemotherapy at disease progression. The primary end point was the disease stabilization rate after 12 weeks of gefitinib (DSR 12). Association of response with molecular markers was examined and longitudinal quality-of-life (QoL) patterns were assessed.

patients and methods

eligibility criteria

Patients with histologically or cytologically confirmed, chemotherapy-naive, inoperable stage IIIB/IV NSCLC and measurable disease (Response Evaluation Criteria in Solid Tumors criteria [11]) were eligible. Eligibility criteria included age >18 years, PS World Health Organization (WHO) of zero to one, adequate bone marrow function, normal kidney function and adequate liver function. Patients could only be included if the local investigator felt it to be clinically safe to withhold standard chemotherapy for 6 weeks. Patients with symptomatic and/or untreated brain metastases and patients with evidence of active interstitial lung disease were excluded. Not allowed was the use of phenytoin, carbamazepine, rifampicin, barbiturates or St Johns Wort. The study was conducted according to the guidelines of Good Clinical Practice [13], the Helsinki Declaration [12] and Swiss regulatory authorities requirements [14, 15] and was approved by the ethic committees of all participating institutions.

treatment

Gefitinib 250 mg/day p.o. was given until documented disease progression, unacceptable toxicity or patient's refusal. After disease progression, chemotherapy was initiated with gemcitabine 1250 mg/m^2 (30 min) on days 1, 8 and cisplatin 80 mg/m^2 (60 min) on day 1, repeated every 3 weeks for up to six cycles. Chemotherapy was stopped early in the case of disease progression, unacceptable toxicity or patient's refusal. Steroids and 5-hydroxytryptamine-3 antagonists were recommended for antiemetic prophylaxis. Prophylactic granulocyte colony-stimulating factor or erythropoietin was given only after febrile neutropenia or anemia. In case of peripheral neuropathy, hearing impairment or renal insufficiency, cisplatin was replaced by carboplatin area under the curve 5 (30 min). Standard dose modifications for toxicity were foreseen.

assessments

Baseline assessments included medical history and smoking habits, computed tomography (CT) scan of thorax/abdomen, bone scan and magnetic resonance imaging (or CT) of the brain (in case of neurologic symptoms). During gefitinib treatment, a physical examination and hematologic and biochemical testing were done at baseline and every 3 weeks until week 12, then every 6 weeks. QoL questionnaires were completed at week 0, 3, 6, 12, 18 and every 12 weeks thereafter. CT scans were repeated at week 6, 12, 18 and every 12 weeks thereafter. Before chemotherapy, new baseline assessments including QoL were obtained. During chemotherapy, hematological values were measured weekly and blood chemistry at each cycle. QoL questionnaires were completed at day 1 of cycle 3 and 5. CT scans were repeated after cycle 2, 4 and 6. During follow-up, physical examination, blood tests, QoL questionnaires and CT scans were scheduled every 12 weeks. After disease progression (RECIST criteria [11]), survival status was assessed every three months.

Adverse events (AEs) were assessed at each patient contact and reported according to National Cancer Institute—Common Terminology Criteria version 3. Relation to trial treatment was graded in five categories and listed as toxicity if at least possibly related to trial treatment.

For all patients responding or with stable disease (SD) after 6 or 12 weeks, CT scans were centrally reviewed by a panel of independent radiologists.

statistical considerations

The primary end point was DSR12 under gefitinib. Secondary end points included objective response, time to progression (TtP), QoL and AEs under either treatment, DSR under chemotherapy and overall survival (OS).

The sample size was estimated using Simon's two-stage optimal design [16] for a 5% type 1 error probability, 90% power, promising and unpromising DSR12 of 50% and 30%, respectively. As accrual was expected to be fast, the stage 1 stopping rule was modified by Herndon's approach [17]. The stage 1 analysis was carried out on the basis of data of 24 patients and indicated continuation of the trial. Gefitinib would be considered promising for further investigations if at least 26 of 63 patients reach disease stabilization (DS) at 12 weeks.

Univariate associations between DS12 and binary covariables were investigated by two-sided Fisher's exact tests. The combined influence of these covariables on DS12 was investigated by a multiple logistic regression. The survival functions and medians of TtP and OS were estimated by Kaplan–Meier's method. OS between strata defined by selected covariables were compared by log-rank tests. The joint association between these covariables and OS was investigated by Cox regression. All tests were of exploratory nature without adjustment for multiple testing. Data analysis were carried out using SAS 9 (SAS Institute Inc., Cary, NC. und Insightful Corp., Seattle, Washington, USA.)

translational research

Specimens were reviewed (LB) and classified according to WHO criteria [18]. Molecular analysis was carried out on unstained tissue sections (4 μm) or Papanicolaou-stained cytological specimens.

Laser microdissection and DNA sequence analysis: at least 80 tumor cells were captured by a laser microdissection system [19] in a tube containing 80 mcl 1× PCR buffer. In all, 20 μl proteinase K was added and incubated overnight at 56°C. PCR conditions were activating of the *Taq* polymerase 95°C for 11 min, 50 cycles of 95°C for 20 s, 59°C for 10 s, 72°C for 50 s, followed by 4 min at 72°C. In all, 0.5 μl of the product of the first PCR was used for the second semi-nested multiplex PCR.

Primers (not shown) were digested in a PTC-100 thermocycler (BioConcept, Allschwil, Switzerland). Sequencing PCR was carried out using the BigDye Terminator v1.1 kit (Applied Biosystems, Rotkreuz, Switzerland).

Experimental condition of the 80 cycles of linear amplification is as follows: denaturation 10 min at 95°C; annealing 10 s at 55°C and elongation 4 min at 60°C. Flowable polymers were used to dynamically coat capillaries. Split argon laser beam allows simultaneous illumination of the 16 capillaries from both sides at the detection cell. Fluorescence signal emitted from the DNA fragments were collected on Charge-coupled device (CCD) camera and visualized using the sequencing analysis software 5.2 (Applied Biosystems).

FISH analysis

Locations of carcinoma cells were saved by a relocation software (Mark&Find Module, Carl Zeiss Vision GmbH, Halbermoos, Germany) and an automated stage (Type 00-24-473-0000, Carl Zeiss AG, Oberkochen, Germany) before hybridization.

LSI EGFR SpectrumOrange/CEP7 SpectrumGreen dual color probe set (Abbott/Vysis, Downers Grove, Illinois, USA) was used. FISH was carried out as previously described [20, 21]. The mean number of scored cells was 96 (±12 cells, range 50–100) in histological specimens and 66.4 (±37.6 cells, range 11–100) in cytological specimens.

quality of life

QoL and disease-related symptoms were assessed by the Functional Assessment of Cancer Therapy-Lung (FACT-L) scale [22, 23]. The self-reported questionnaire comprises four general subscales (physical, functional, social and emotional well-being) and one lung cancer symptom-specific subscale (LCS). The trial outcome index (TOI) is derived by adding scores of the physical well-being and the functional well-being subscales and the LCS.

Questions are answered on a five-point scale ranging from 'not at all' (0) to 'very much' (4). Maximum scores are 28 for LCS, 84 for TOI and 136 for FACT-L, respectively. Higher scores indicate better QoL or fewer symptoms [24]. For each time point and QoL score, the median value of the difference from baseline was evaluated. Due to decreasing number of patients over time the analysis remains descriptive. Only QoL forms completed at the scheduled visits or up to 7 days before were included into the analysis. For patients with NSCLC, a difference of 2–3 points in LCS score and a difference of 5–7 points in TOI are considered as clinically relevant [25].

results

From November 2003 to October 2004, 63 patients were included. Patient characteristics are summarized in Table 1.

Table 1. Patient characteristics

n	63
Age	
Median	62 years
Range	39–85 years
Gender	
Female	24 (38%)
Male	39 (62%)
Stage	
IIIB	14 (22%)
IV	49 (78%)
Histology	
Adenocarcinoma	27 (43%)
Bronchioloalveolar carcinoma	5 (8%)
Squamous cell carcinoma	13 (21%)
NSCLC NOS	18 (29%)
ECOG performance status	
0	36 (57%)
1	27 (43%)
Metastatic sites	
Lung	37
Bone	22
Adrenal glands	18
Liver	6
Brain	3
Other (soft tissue, spleen)	3

NSCLC, non-small-cell lung cancer; NOS, not otherwise specified; ECOG, Eastern Cooperative Oncology Group.

response

gefitinib. All 63 patients started gefitinib treatment and were assessable. Median treatment duration was 2.5 (0.1–21.2) months. Investigator reported objective responses at week 12 were 1 complete remission (CR), 5 partial remissions (PRs) and 18 SDs, resulting in an objective RR of 9.5% and a DSR12 of 38% [exact 95% confidence interval (CI) 26.2% to 51.2%]. Independent radiological review was carried out in 26 cases having shown a stabilization of disease according to local investigators. Investigator's assessments were confirmed in 16 and could not confirm DS in 8 and PR in 1, and in 1 patient CR was changed to PR. With reviewed results, 15 patients reached DS with DSR12 of 24% (exact 95% CI 12.9% to 38.8%). Table 2 shows response data for all 63 patients with reviewed results where applicable. Reason for stopping gefitinib was progression in 49 patients, clinical deterioration in 4, death in 8 (7 due to tumor and 1 lung embolism) and nonfatal serious AE in 1 (perforated appendicitis). One patient was still on gefitinib at the time of analysis.

DS12 was associated with smoking status [$P = 0.031$, odds ratio (OR) = 0.186] and *EGFR* mutation status ($P = 0.037$, OR = 12.3). A multiple logistic regression model confirmed the association between *EGFR* mutation status and DS12 (Table 3). There was no significant association between DS12 and the other factors investigated.

chemotherapy. In all, 41 patients started chemotherapy. Reasons for not receiving chemotherapy were death ($n = 8$), poor PS (4), refusal (3), investigators decision (2), irradiation for cerebral metastases (2), serious AE (perforated appendicitis, 1), chemotherapy in a different hospital (1) and continuation of gefitinib (1). Totally, 171 cycles were administered (1–6, median five cycles per patient). In all, 20 patients received six courses. PR was achieved in 14 patients and SD in 15 patients for an overall RR of 34.1% and a DSR of 70.7%. Three patients were not assessable (two stopped therapy for toxicity before first assessment and one not assessed due to treatment delay).

survival analysis

Median follow-up time of the 15 patients still alive was 21.6 months. OS (Figure 1) and TtP are detailed in Tables 2. Median TtP under post-gefitinib chemotherapy, calculated from day 1 of chemotherapy, was 6.8 months for the 41 patients with chemotherapy and 4.8 months for all the 63 patients.

According to the univariate analysis for FISH, *KRAS*, *EGFR*, age (≥/<65 years), gender, PS (0/1), smoking status (never/smoker), adenocarcinoma, skin toxicity and disease stage, only patients experiencing any skin toxicity to gefitinib had significantly different survival ($n = 63$, $P = 0.022$); the corresponding multiple Cox model (without FISH, *KRAS* and *EGFR*) found no statistically significant covariables.

toxicity

In all, 61 patients were assessable. Two patients were not assessable due to death (tumor/lung embolism) before 4 weeks of treatment. Grade III toxic effects during gefitinib were one

Table 2. Response to gefitinib week 10–12 after independent radiological review (all study patients)

	n	PR	SD	PD	Early death	RR %	DSR %	TtP (months)	OS (months)
All patients	63	5	10	43[a]	5[b]	7.9	23.8	2.5	11.4
Never smokers	9	4	1	4	0	44.4	55.6	9.4	20.2
Females	24	3	2	17	2	12.5	20.8	2.1	12.0
Adenocarcinoma	32	2	5	21	4	6.3	21.9	1.6	9.4

[a]Including one patient with clinical deterioration only.
[b]Four early deaths due to tumor without documented PD, one lung embolism.
PR, partial remission; PD, Progressive Disease; SD, stable disease; RR, response rate (intention-to-treat analysis); DSR, disease stabilization rate (intention-to-treat analysis); TtP, median time to progression (weeks); OS, median overall survival.

Table 3. Univariate analysis and multiple logistic regression of reviewed DSs at week 12 of gefitinib

	n	PR	SD	PD	Early death	RR %	DSR %	TtP (months)	OS (months)
All patients	57	3	10	40[a]	4	5.3	22.8	2.4	11.4
EGFR mutation positive	4	2[b]	1[c]	1[c]	0	50	75	7.5	Not reached
FISH positive	34	3	4	24[a]	3	8.8	20.5	2.3	11.8
KRAS mutation positive	5	0	0	4	1	0	0	2.4	9.0

[a]Including one patient with clinical deterioration only.
[b]In all, 15 bp deletion E746-A750 and 18 bp deletion exon 19.
[c]Both L858R exon 21.
PR, partial remission; SD, stable disease; RR, response rate (intention-to-treat analysis); DSR, disease stabilization rate (intention-to-treat analysis); TtP, time to progression; OS, overall survival; EGFR, epidermal growth factor receptor.

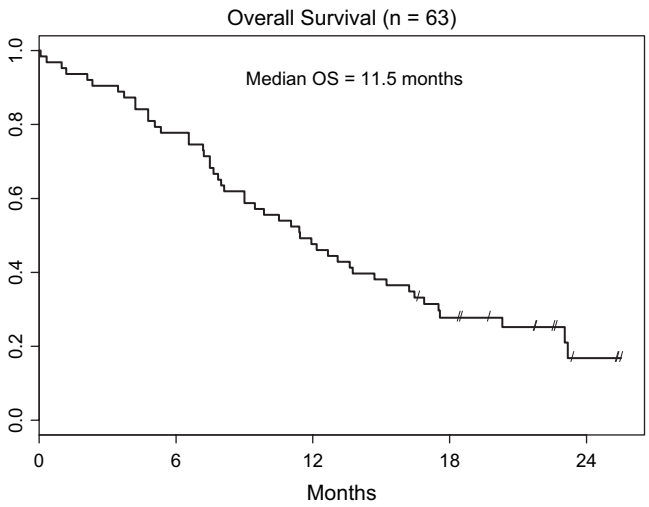

Figure 1. Kaplan–Meier curves for overall survival.

neutropenia, five elevated Alanine-Aminotransferase, one elevated creatinine clearance, Aspartate-Aminotransferase alkaline phosphatase each, one hypoalbuminemia and one hyponatriemia. Nonlaboratory toxic effects grade III were as follows— three patients with diarrhea, and one case of each of the following: dry skin, pruritus, musculoskeletal pain, abdominal pain, neurological symptoms of the legs, deep vein thrombosis and dehydration. No grade IV/V toxic effects were observed and no patient stopped gefitinib due to toxicity. In 36 patients (59%), skin toxicity of any grade was reported; no interstitial lung disease was seen.

chemotherapy. All 41 patients receiving chemotherapy were assessable for toxicity. Grade III events: fatigue and infection in three patients, mucositis, diarrhea, vomiting, cardiac problems in two patients each, nausea, anorexia, hearing loss, glaucoma, weakness, confusion, renal failure and hyperbilirubinemia in one patient each. Grade III/IV toxicity: neutropenia in 7 of 9 patients, thrombocytopenia in 13 of 11 patients. Further, one lung embolism and one Syndrome of Inadequate ADH-Secretion grade IV were reported.

translational analyses

In all, 57 patients consented for molecular analyses (Table 4). Four *EGFR* mutations were detected, two exon 19 deletions (both patients responding to gefitinib) and two L858R mutations on exon 21 (one SD and one Progressive Disease to gefitinib). Clinical and molecular data of these patients are summarized in Table 5. *EGFR* mutations were more frequent in females (2 of 20) than in males (2 of 37) and in never smokers (2 of 6) than in former or current smokers (2 of 51). All patients with *EGFR* mutation were also FISH positive and none had a *KRAS* mutation.

From the 34 patients with high *EGFR* gene copy number (Cappuzzo-criteria [10]), 5 had true *EGFR* gene amplification (none with DS).

Initial FISH analysis was done on cytological material in 20 patients and on histologies in 37. The overall positivity rate was 59% (cytologies 55% and histologies 62%). A blinded FISH reanalysis by a second team was carried out in 47 samples (10 samples with bleached fluorescent signals).

Rescoring confirmed initial results in all 14 cytology samples, whereas 7 of the 20 histology specimens initially scored positive were retested negative.

quality of life

QoL forms submission rate was 100% at start of treatment, 80% at gefitinib week 6 (44 received and analysed/55 expected) and 84% (27/32) at week 12. At the initiation of chemotherapy, submission rate was 63% (26/41), and 50% (14/28) and 43% (10/23) at week 6 and 12, respectively. Main reasons for missing forms were that the questionnaire was not presented to the patient or not completed at the due time point.

Median QoL scores are shown in Table 6. No associations between responses to gefitinib and QoL scores were observed. At week 12 of gefitinib, 29%, 15% and 41% of patients had relevant improvements of FACT-L, TOI and LCS, respectively, and 54%, 62% and 33% remained stable (percentage on the basis of patients with available data). During chemotherapy at week 12, 43%, 29% and 43% reported improvement and 28%, 43% and 43% stabilization.

discussion

The primary end point of this trial of first-line gefitinib treatment in advanced NSCLC was DSR12. With 24% of patients not progressing at 12 weeks, the treatment did not meet the predefined criteria for further investigation. Although the study proved first-line gefitinib to be a safe strategy with OS times comparable to up-front chemotherapy, a potential benefit of the sequential strategy most probably could only be

Table 4. Reviewed response by molecular analysis (patients consenting for molecular analyses only)

Site	Material	Histological type	EGFR mutation	KRAS (exon 2)	FISH status (Cappuzzo et al. [10])
Lymph node	Biopsy	SqCLC	L858R in exon 21	Negative	High polysomy
Lung	Biopsy	AC	L858R in exon 21	Negative	High polysomy
Lung	Biopsy	NSCLC NOS	18 bp deletion in exon 19 (L747-S752)	Negative	High polysomy
Lung	Cytology	NSCLC NOS	15 bp deletion in exon 19 (E746-A750)	Negative	High polysomy

AC, Adenocarcinoma; EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; NOS, not otherwise specified; SqCLC, Squamous Cell Carcinoma.

Table 5. Characteristics of EGFR-mutated samples

	Gefitinib baseline	Gefitinib week 6	Gefitinib week 12	Chemo baseline	Chemo week 6	Chemo week 12
FACT-L	96 (53–135)	96 (65–136)	96 (50–136)	87 (61–132)	105 (76–134)	107 (76–135)
n	63	42	24	23	14	10
TOI	62 (31–83)	55 (26–84)	59 (31–84)	49 (28–81)	62 (45–82)	65 (32–83)
n	63	44	27	24	14	10
LCS	21 (10–27)	21 (7–28)	21 (15–28)	17 (10–27)	24 (14–27)	24 (15–27)
n	63	44	27	25	14	10

QoL, quality of life; Chemo, chemotherapy; FACT-L, Functional Assessment of Cancer Therapy-Lung; TOI, trial outcome index; LCS, lung cancer symptom-specific subscale.

Table 6. Median (range) of QoL scores

Variable	*n*	DS	No DS	*P* value (univariate)	*P* value (logistic regression, *n* = 53)
Age ≤65/>65 years	63	7/8	29/19	0.3838	0.29
Sex female/male	63	5/10	19/29	0.7665	0.05
Performance status 0/1	63	11/4	25/23	0.232	0.07
Stage IIIB/IV	63	3/12	11/37	1	0.12
Smoking never/ever	62	5/10	4/34	0.0308	0.34
Other histologies/adenocarcinoma	63	8/7	23/25	0.7735	0.69
Skin toxicity no/yes	63	4/11	23/25	0.232	0.61
FISH negative/positive	54	5/7	15/27	0.7435	0.36
KRAS wild type/mutation	55	12/0	38/5	0.5743	0.41
EGFR wild type/mutation	55	10/3	41/1	0.0373	0.02

DS, disease stabilization; EGFR, epidermal growth factor receptor.

found in selected patient groups. A benefit in these patients could be an improvement of treatment efficacy or related to QoL through the avoidance of chemotherapy toxicity.

A trial testing first-line erlotinib in a nonenriched group of NSCLC patients was presented in 2006 by Giaccone et al. [26]. A nonprogression rate of 53% after 6 weeks of treatment was reported, identical to our data for the 6-weeks time point. Jackman et al. [27] in 2007 reported on first-line erlotinib in elderly patients and found comparable results: 10% PR and additional 41% SD after 2 months. These as well as our results indicate that TKI's have comparable activity in first-line use as in pretreated patients. Further, first-line TKI trials were reported by Asian authors, partially with frequent occurrence of interstitial lung disease [28]. Lee et al. [29] reported on a phase II study in Asian never-smoking patients with adenocarcinoma and found impressive results with 69% PR and additional 11% SD.

We have seen best outcomes in response as well as survival times in never smokers and in *EGFR* mutation carriers (exon 19 deletion or exon 21 L858R point mutation). Among the four, *EGFR*-mutated tumors response was restricted to those with exon 19 deletions. This lends support to previous evidence indicating that exon 19 deletion is the most predictive *EGFR* mutation type [30]. As previously shown, *KRAS* mutations are mediators or indicators of resistance to gefitinib [31].

In contrast to earlier publications, FISH analysis of *EGFR* copy number (true amplifications and 'high polysomy' according to Cappuzzo criteria [10]) did not correlate with clinical outcomes. This discrepancy could be due to the small number of patients in this study, but may also be explained to some degree by interobserver variation in FISH scoring. In fact, reanalyses of the histology specimens by a second team showed low reproducibility of the results. There is a need to quantify the problem of inter- and intraobserver variabilitiy in the detection of high polysomy of the *EGFR* gene in appropriately sized patient series, as such data do not yet exist in the literature.

According to our results, patients would be best selected for TKI treatment according to smoking status and to *EGFR* or *KRAS* mutation status. In the univariate analysis, patients experiencing skin toxicity had significantly longer survival; this correlation was not uniformly reported in earlier series and was not confirmed in our multivariate analysis. The emergence of skin rash may be influenced by the duration of treatment as well.

Gefitinib was very well tolerated and no patient stopped gefitinib due to toxicity. QoL levels were maintained during gefitinib treatment, declined at disease progression and increased again during chemotherapy. Because only nonprogressors completed QoL forms during chemotherapy and the number of evaluable forms was low, analyses remained descriptive and should be interpreted with caution. QoL compliance was low due to organizational problems rather than to patient-related factors.

The primary end point (DSR12) was verified by an independent radiological review which significantly altered response results; DSR12 was corrected from 38% as per investigators' reports to 24% after review, thus underscoring the importance of independent evaluations in this type of trials.

In conclusion, gefitinib first-line therapy did not reach the predefined efficacy boundaries for further investigation in this setting. Compared with the results from trials of up-front chemotherapy, patients pretreated with gefitinib reached similar survival times. Furthermore, gefitinib showed comparable efficacy in first-line use as in pretreated patients and stabilized QoL in nonprogressing patients. First-line use should further be investigated in patients selected according to smoking history or mutational status including *EGFR* and *KRAS* and should include QoL analyses.

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